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(c) Potts, K. T.; Dery, M. O. *JOC* 1990, 55, 2284. (d) Potts, K. T.; Rochampruk, T.; Coats, S. J.; Hadjariapoglou, L.; Padwa, A. *JOC* 1993, 58, 5040. (e) Burner, S.; Canestor, R.; Widmer, U. H. *JOC* 1994, 57, 239.

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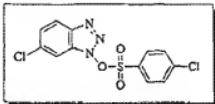
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6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole



[57320-65-7]

C₁₃H₉Cl₂N₃O₅S

(MW 344.17)

(reagent for active ester formation;¹ synthesis of amides;¹ esters;² thiol esters³ from carboxylic acids; peptide synthesis⁴)

Physical Data: mp 125–127 °C.

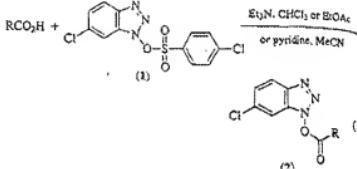
Preparative Method: prepared by reaction of 6-chloro-1-hydroxybenzotriazole with *p*-chlorobenzenesulfonyl chloride in 1M aqueous NaOH/ether.

Purification: recrystallization from benzene/petroleum ether.

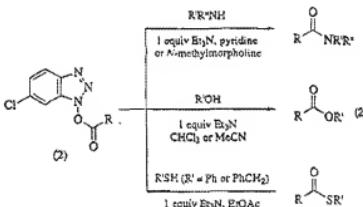
Handling, Storage, and Precautions: stable for long periods in the absence of moisture and light.

Active Ester Formation. 6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole (1) converts carboxylic acids to the 1-acyloxybenzotriazole derivatives (2) in good yield (eq 1).¹ A study of several related reagents found (1) to be most suitable based on overall considerations of reactivity, stability, and accessibility. The reaction occurs rapidly (usually less than 1 h) in the presence of one equivalent of *Triethylamine* in CHCl₃ or EtOAc; the more polar solvent MeCN is required if *Pyridine* is used as base. The active esters (2) can generally be isolated as stable, crystalline solids.

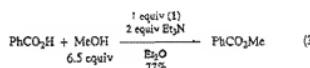
The active esters (2) react readily in the presence of base with amines,¹ alcohols,² and certain thiols³ to provide amides, esters, and thioesters, respectively (eq 2). Aminolysis is generally rapid, as is reaction with primary alcohols; use of secondary al-



cohols such as *i*-propanol requires higher temperature (boiling CHCl₃), while no reaction is observed between (2) and *t*-butanol.

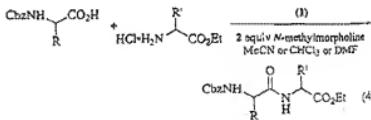


Ester formation may also be achieved without isolation of (2) by mixing a carboxylic acid and an alcohol with (1) in the presence of two equivalents of base (eq 3).² Formation of the 1-alkoxy-6-chlorobenzotriazole as byproduct is suppressed by the use of ether as solvent rather than CHCl₃; use of pyridine in MeCN is also suitable.



Similarly, one-pot amide synthesis is possible;⁴ formation of sulfonamide by direct reaction of (1) with amine is avoided by using *N*-methylmorpholine or pyridine as base instead of Et₃N.¹

Peptide Synthesis. This method of amide bond formation has been used for peptide synthesis; the active ester is usually reacted with the amino component in situ (eq 4).¹



These reaction conditions have advantages over the popular *1,3-Dicyclohexylcarbodiimide* (DCC) method, not least that the sulfonic acid and hydroxybenzotriazole co-products can be washed out with aqueous sodium bicarbonate. In the coupling of *N*-protected *L*-asparagine or *L*-glutamine with amino compo-

ents, no dehydration of the side-chain amide (to the nitrile) was observed. Free hydroxy or imino groups do not cause problems, as shown by the successful preparation of serine-, tyrosine- and histidine-containing peptides.

Using the coupling of Cbz-Phe-Ile-OH with H-Pro-OBn in DMF as a test, the degree of racemization using (1) with various bases was compared with other methods; less racemization occurred using (1) than with DCC.^{1b} A more extensive comparison of degree of racemization has also been reported.⁴

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- Itoh, M.; Hagiwara, D.; Notani, J. *S* 1975, 456.
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Chlorocyanoketene¹



[60010-89-1]

C₃CINO

(MW 101.49)

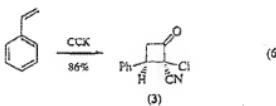
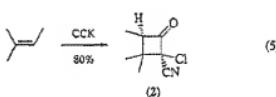
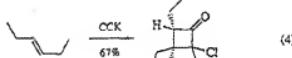
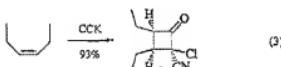
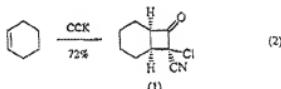
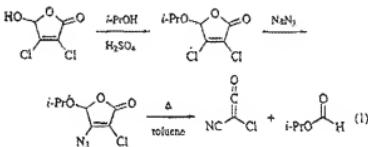
functions as a potent electrophile in reactions with a wide variety of ketenophiles including alkenes,² alkynes,⁴ arylaldehydes,⁵ and imines⁶⁻⁸)

Alternate Name: CCK.

Preparative Methods: chlorocyanoketene readily undergoes self-condensation and must be generated *in situ* prior to usage. By generating the ketene in the presence of a ketenophile, concentration-related difficulties are circumvented and yields are greatly improved.² A most convenient route to the title compound is afforded by the thermal decomposition of pseudo esters of azidofuranones. Starting with commercially available mucochloric acid the desired furanone is synthesized in a two-step process: etherification and azidation (eq 1). Alcohols with at least three carbons, such as isopropanol, are desirable for the etherification in order to minimize the detonation capability of the subsequent azide.²

Cycloadditions to Alkenes. Cycloadditions of chlorocyanoketene (CCK) to alkenes give good yields of the corresponding cyclobutanones and include additions to di-, tri-, and tetrasubstituted alkenes. The addition process is in complete accord with a concerted $\text{2}_a + \text{2}_a$ mechanism. Cyclobutanones (1), (2), and (3) are obtained by a highly stereoselective route as

evidenced by the formation of their respective single diastereomers (eqs 2-7).



Alkenic ketenophiles with higher nucleophilic character react with CCK in a dipolar fashion. For example, treatment of cyclopentadiene with CCK gives a 55:45 mixture of diastereomers (eq 8). Further exemplifying this dipolar mode is the reaction of the ketene with dihydropyran (eq 9), whose product likely arises from a proton transfer process involving a zwitterionic intermediate.³

